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10/052,803	11/07/2001	Fernand Labrie	P/1259-637	3989

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EXAMINER

JIANG, SHAOJIA A

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 08/13/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/052,803

Applicant(s)

LABRIE, FERNAND

Examiner

Shaojia A Jiang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 April 2003 and 14 May 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
- 4a) Of the above claim(s) 6-11, 21, 24 and 28-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 12-20, 22, 23, 25-27 and 34-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3, 5, 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

This application is a continuation of 09/771,180 (now abandoned), which claims priority to provisional application Serial No. 60/178,601.

Applicant's preliminary amendment filed on April 21, 2003 in Paper No. 7 is acknowledged wherein the instant specification has been amended as to page 25 lines 6-20, and page 69-70, Table 8.

Currently, claims 1-43 are pending in this application.

### ***Election/Restrictions***

Applicant's election without traverse of the species of EM-652.HCl in claims 19 and 41 for the SERM compound, 17 $\beta$ -estradiol in claim 20 for as an estrogen, and dehydroepiandrosterone (DHEA) for additional agent in claim 2, in Paper No. 8 submitted May 14, 2003 is acknowledged.

The claims have been examined insofar as they read on the elected specie. Claims 1-5, 12-20, 22-23, 25-27, and 34-43 read on the elected species and will be examined on the merits herein.

Claims 6-11, 21, 24, and 28-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 22-23, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular selective estrogen receptor modulator (SERM) compounds having the formula in claims 12-16 herein and the particular estrogens in claim 20, further in combination with the particular additional agents herein in the claimed composition, does not reasonably provide enablement for any selective estrogen receptor modulator and any estrogens, recited in the claims herein.

The recitations, "one selective estrogen receptor modulator" and "one estrogen", are seen to be merely functional language.

Even regarding the recitation for compounds in claims 3-5 and 25-27, one skilled in the art would clearly recognize that the recitation would encompass numerous compounds containing various structurally different substituents.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

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(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a pharmaceutical composition for therapeutic treatments.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since the broadest claims (i.e., claims 1-2) reads on any "selective estrogen receptor modulator" and "estrogen" employed in the composition herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

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In the instant case, "one selective estrogen receptor modulator" and "one estrogen" recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for each kind of functional compounds for the composition in claims.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would

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be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) the **combination** of any compounds represented by "one selective estrogen receptor modulator" and "one estrogen", which may encompass more than a thousand compounds. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9<sup>th</sup> ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

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The presence or absence of working examples and the quantity of experimentation necessary:

As discussed above, only those particular compound for each kind of functional compounds employed in the composition herein is disclosed in the specification.

Moreover, it is noted that the specification merely provides the testing of two particular SERMs (i.e., EM-652 and EM-800) in working examples of the instant specification.

Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the compounds in the claimed composition. See MPEP § 716.02(d).

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

*Genentech*, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test all compounds encompassed in the instant claims and their



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combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 12-20, 22-23, 25-27, and 34-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations, "derivative" and "derivatives" in claims 1-2 and 22-23 render claims 1-5, 12-20, 22-23, 25-27, and 34-43 indefinite. The recitations, "derivative" and "derivatives" are not defined in the specification. Hence, one of ordinary skill in the art could not interpret the metes and bounds as to "derivative" and "derivatives", in the claim. Therefore, the scope of claim is indefinite as to the composition encompassed thereby.

The expressions " R100 is a bivalent moiety....B-ring by.." render claims 12-18 and 34-40 indefinite. The expressions " R100 is a bivalent moiety....B-ring by.." are not understood since "R100" is not recognized as to a chemical moiety and there is insufficient antecedent basis for the limitation, B-ring, in the claim.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 12-20, 22-23, 25-27, and 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. ("54", PTO-1449 submitted November 7, 2001 in Paper No.5) and Barrett-Connor et al. ("4", PTO-1449 submitted November 7, 2001), and Do Nascimento (PTO-892) in view of Labrie et al. (WO 96/26201, PTO-1449 submitted November 7, 2001)

Luo et al. discloses that an estrogen, DHEA alone, or the particular SERM (antiestrogen), EM-800 alone (having 2S configuration and moieties convertible in vivo to hydroxyl), is known to be useful in a method of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels. See abstract and page 4436 Fig. 1 "Structure of EM-800", page 4438 the left column "Effect on serum lipid levels". Luo et al. further discloses that the combination of DHEA and EM-800 exerts more potent effect on reducing serum lipid levels than each compound used alone (page 4438 the left column "Effect on serum lipid levels" and page 4439 Fig. 4, and page 4443 the left column.

Barrett-Connor et al. teaches that SERMs are capable of lowering serum lipid levels to reduce the risk of coronary heart disease, as estrogen does. See abstract.

Do Nascimento teaches that the particular estrogen, 17 $\beta$ -estradiol, is useful in treating hypercholesterolemic patients (see abstract).

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The prior art does not expressly disclose the employment of the combination of an estrogen such as  $17\beta$ -estradiol and the particular SERM, EM-652.HCl, or further combining with DHEA in a pharmaceutical composition.

Labrie et al. (WO 96/26201) discloses that both EM-800 and EM-652 are antiestrogens (SERMs), and EM-800 has moieties convertible in vivo to hydroxyl to become EM-652. Thus, EM-800 is a metabolite of EM-652, having the same functional property and activity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ of the combination of an estrogen such as  $17\beta$ -estradiol and the particular SERM, EM-652.HCl, or to further combine with DHEA, in a pharmaceutical composition.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the combination of an estrogen such as  $17\beta$ -estradiol and the particular SERM, EM-652.HCl, or to further combine with DHEA, in a pharmaceutical composition, since estrogens such as  $17\beta$ -estradiol and DHEA are well known in the art to be used in methods of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels according to the cited prior art herein. Moreover, the particular SERM, EM-800, a known metabolite of EM-652 (convertible in vivo to hydroxyl to become EM-652), alone or in combination with an estrogen such as DHEA, is known to be useful in a method of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels according to Luo et al.

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Therefore, one of ordinary skill in the art would have reasonably expected that combining an estrogen such as  $17\beta$ -estradiol and the particular SERM, EM-652.HCl, or further combining with DHEA, all known useful for the same purpose, i.e., treating hypercholesterolemia, would improve the therapeutic effects for treating the same disorder, hypercholesterolemia, and/or would produce additive therapeutic effects in treating the same. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) regarding combination inventions. It is considered prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose.

Further, the teachings of Luo et al. that the combination of DHEA and EM-800 exerts more potent effect on reducing serum lipid levels than each compound used alone clearly provides the motivation of the instant claimed method employing the combination of EM-652,  $17\beta$ -estradiol and DHEA.

Furthermore, one of ordinary skill in the art would have been motivated to prepare a kit comprising the same composition because the preparation of a kit comprising a pharmaceutical composition is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.


In view of the rejections to the pending claims set forth above, no claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.



S. Anna Jiang, Ph.D.  
Patent Examiner, AU 1617  
July 31, 2003